A Randomized Phase 2 Study Of Ganetespib, A Heat Shock Protein 90 Inhibitor, In Combination With Docetaxel in Second-Line Therapy Of Advanced Non-Small-Cell Lung Cancer (GALAXY-1)

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Key Message:

The randomized Phase 2 study of ganetespib in combination with docetaxel (GALAXY-1) aimed to evaluate efficacy and safety in advanced NSCLC, and to identify patient populations most likely to benefit from the combination. The study did not meet its primary endpoints. Significant prolongation of OS and PFS was observed in patients >6 months from diagnosis of advanced lung adenocarcinoma, the subgroup chosen as the target population for the Phase 3 study (GALAXY-2).

Key Words: ganetespib, docetaxel, advanced NSCLC, adenocarcinoma, HSP90 inhibitor

Abstract

Background: To evaluate the activity and safety of ganetespib in combination with docetaxel in advanced NSCLC and to identify patient populations most likely to benefit from the combination.

Patients and Methods: Patients with one prior systemic therapy for advanced disease were eligible. Docetaxel (75mg/m^2 on Day 1) was administered alone or with ganetespib (150mg/m^2 on Days 1 and 15) every 3 weeks. The primary endpoints were progression-free survival (PFS) in 2 subgroups of the adenocarcinoma population: patients with elevated lactate dehydrogenase (eLDH) and mutated KRAS (mKRAS).

Results: Out of 385 patients enrolled, 381 were treated. Early in the trial increased hemoptysis and lack of efficacy were observed in non-adenocarcinoma patients (n=71), therefore only patients with adenocarcinoma histology were subsequently enrolled. Neutropenia was the most common grade ≥3 adverse event: 41% in the combination arm vs. 42% in docetaxel alone. There was no improvement in PFS for the combination arm in the eLDH (*N*=114, adjusted HR=0.77, *P*=0.1134) or mKRAS (*N*=89, adjusted HR=1.11, *P*=0.3384) subgroups. In the ITT adenocarcinoma population there was a trend in favor of the combination, with PFS (*N*=253, adjusted HR=0.82, *P*=0.0784) and overall survival (OS) (adjusted HR=0.84, *P*=0.1139). Exploratory analyses showed significant benefit of the ganetespib combination in the prespecified subgroup of adenocarcinoma patients diagnosed with advanced disease >6 months before study entry (*N*=177): PFS (adjusted HR=0.74, *P*=0.0417); OS (adjusted HR=0.69, *P*=0.0191).

Conclusion: Advanced lung adenocarcinoma patients treated with ganetespib in combination with docetaxel had an acceptable safety profile. While the study's primary endpoints were not met, significant prolongation of PFS and OS was observed in patients >6 months from diagnosis of advanced disease, a subgroup chosen as the target population for the Phase 3 study.

Introduction

Ganetespib is a next-generation resorcinol-based small molecule inhibitor of the heat-shock protein 90 (Hsp90), a chaperone protein critical to the stabilization and activation of numerous oncogenic proteins. By targeting Hsp90, ganetespib simultaneously inhibits multiple oncogenic pathways, resulting in reduced tumor growth, metastasis and angiogenesis in preclinical models [1]. In early clinical trials, ganetespib was well tolerated and demonstrated single-agent activity in patients with tumors harboring driver oncogenes such as mutated BRAF and KRAS, EML4-ALK translocations, and in tumors with HER2 overexpression [2-4]. The combination of ganetespib and taxanes is synergistic in preclinical studies [5, 6], possibly due to down-regulation of AKT signaling [7, 8]. It was of interest therefore to evaluate ganetespib in combination with docetaxel in patients with advanced NSCLC. A Phase 1 study [9] established the recommended schedule and doses as docetaxel at 75 mg/m^2 on Day 1 and ganetespib at 150 mg/m^2 on Days 1 and 15 of each 3-week cycle. The most common adverse events (AEs) associated with combination therapy were diarrhea, fatigue, neutropenia, and anemia. There was a strong scientific rationale for evaluating ganetespib in patients with baseline elevated LDH (eLDH) levels and those with mutated KRAS (mKRAS). eLDH is a prognostic factor in NSCLC [10, 11]. The LDH subunit A (LDH-A) expression is regulated by HIF1α [12-14], a master transcription factor overexpressed in tumors with aggressive and treatment-resistant phenotypes [15, 16]. Therefore, eLDH might represent a surrogate biomarker for increased HIF1α tumor levels. Ganetespib decreased HIF1α expression in tumors both in preclinical models and in biopsies from ganetespib-treated rectal cancer patients [17].

Several RAS effectors are Hsp90 clients including proteins in the MAPK pathway (ARAF, mutant BRAF, CRAF, p-ERK2, the MAPK agonist COT), and the PI3K/AKT signaling cascade (AKT, PDK1, p70S6K) [18, 19]. In a recent clinical study of ganetespib monotherapy in advanced NSCLC, 7/13 evaluable patients with mKRAS tumors had stable disease and transient tumor shrinkage [3]. Taken together, these considerations provide considerable support for evaluating ganetespib in patients with tumors harboring mutated KRAS.

GALAXY-1, a large, randomized Phase 2 study, was designed to determine whether ganetespib could enhance the efficacy of docetaxel in advanced NSCLC, and to identify patient subsets that would most benefit from this combination-therapy approach.

Patients and Methods

This global, multicenter, open-label, randomized Phase 2 study evaluated ganetespib in combination with docetaxel (combination arm) versus docetaxel alone (control arm) in patients with advanced NSCLC. An interim data review identified a safety signal of increased hemoptysis and lack of efficacy in non-adenocarcinoma patients, and therefore the eligibility criteria were amended to include only patients with adenocarcinoma histology. Key inclusion criteria were: Stage IIIB or IV NSCLC (AJCC Cancer Staging Manual 7th edition), ECOG performance status (PS) of 0 or 1, and disease progression following first-line therapy. Prior maintenance therapy was allowed. Patients with treated and stable brain metastases were eligible. Adequate hematology laboratory values and organ function were required for inclusion. Women of childbearing age were required to have a negative serum pregnancy test. Evaluation of EGFR mutational status and ALK translocation status was not required at study entry. Patients were excluded if they had serious cardiac illness, baseline QTc interval of >470 msec on

electrocardiogram, uncontrolled high-risk arrhythmias, radiotherapy within 2 weeks before randomization, major surgery within 4 weeks before randomization, hemoptysis >grade 2 at randomization, or history of hypersensitivity to docetaxel. Patients with uncontrolled intercurrent illness and pregnant or lactating women were also excluded. The local institutional review board at each participating site approved the study protocol.

Study treatment

Patients were randomized (1:1) to therapy with ganetespib in combination with docetaxel (combination arm) or docetaxel alone (control arm). Docetaxel was administered at a dose of 75 mg/m^2 as a 1-hour intravenous infusion on Day 1 (D1) of each treatment cycle to patients in both treatment arms. Ganetespib was given at a dose of 150 mg/m^2 as a 1-hour intravenous infusion on D1 and D15 of each treatment cycle to patients receiving combination therapy. On days when both drugs were given, administration of ganetespib preceded docetaxel with a 1-hour interval between infusions. Loperamide was used as prophylaxis against diarrhea in the combination group. Treatment cycles were repeated every 3 weeks. Study treatment was continued until disease progression, unacceptable toxicity, or withdrawal of informed consent. For patients in the combination arm, docetaxel could be discontinued after 4-6 cycles and before progression of disease per investigator discretion. Maintenance treatment with ganetespib monotherapy could continue until progressive disease, toxicity, or patient's withdrawal. Crossover between the treatment arms was not allowed. Treatment beyond progression was allowed in both arms if the patient continued to derive clinical benefit. Supportive care measures such as bisphosphonates and growth factors were allowed according to local guidelines.

Study assessments

Eligibility for inclusion was assessed within 4 weeks prior to randomization. Baseline assessments included medical history, documentation of prior anticancer therapies, complete physical examination, assessment of PS, serum pregnancy test (if applicable), 12-lead electrocardiogram, and collection of archived tumor tissue. The following laboratory tests were performed as part of screening: complete blood count (CBC) with differential, serum electrolytes, BUN, creatinine, total protein, albumin, amylase, lipase, uric acid, AST, and ALT. Serum total LDH and isoforms were measured in a central laboratory. Imaging studies included computerized axial tomogram (CT) scan of chest, upper abdomen, radionuclide bone scan, and imaging of the brain at baseline. Quality of life was assessed by the European Organization for research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) at baseline and every 6 weeks.

Safety assessments included CBC with differential, serum chemistry tests, and vital signs on D1 and D15 of each cycle; physical exams were performed on D1 of each treatment cycle. Efficacy assessments were performed at Week 3 (for evaluation of treatment effects in rapid progressors), Week 6, and every 6 weeks thereafter. Brain and bone scans were repeated when clinically indicated. Upon end of study treatment, patients underwent a physical exam, assessment of PS, 12-lead electrocardiogram, and review of AEs. For patients who discontinued study treatment for reasons other than progressive disease, imaging studies were repeated every 6 weeks until documented disease progression or initiation of another anticancer treatment regimen. After disease progression, survival information was collected every 6 weeks. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used for efficacy assessment.

Dose modifications

The most common AEs were managed with appropriate supportive care measures, treatment delays, and dose modification of study drugs. Treatment delays were allowed for a maximum of 14 days to allow for resolution of toxicity. At first instance of toxicity, study drugs were dose reduced to 80%. Further dose reductions required discussion with the medical monitor. In general, dose reductions were not performed for Grade 1 or 2 non-hematological toxicity. For Grade 3/4 toxicity, treatment was delayed until resolution to ≤Grade 1 and study drug was resumed with a dose reduction. If toxicity did not resolve despite a 2-week treatment delay, the patient was discontinued from study treatment. The dose of docetaxel was reduced for Grade 2 neuropathy, Grade 3/4 fatigue, Grade 3/4 neutropenia with fever, and elevation of ALT/AST to >3×ULN. Ganetespib dose was reduced for Grade 3/4 fatigue, Grade 3 QTc prolongation, or elevation of ALT/AST >3×ULN. The study required that medications associated with a high incidence of QTc prolongation be avoided or used with caution. Similarly, substrates of CYP3A4 and CYP2C19 were to be avoided.

Statistical design

The original study design had a primary endpoint of PFS in all enrolled advanced NSCLC patients. As interim data became available, an increased rate of hemoptysis was observed in patients with non-adenocarcinoma histology and the protocol population was changed to patients with lung adenocarcinoma histology. Two populations were identified as populations of interest: patients with eLDH and patients with mutated KRAS, based on biological rationale and preclinical and clinical data. The primary endpoints of the study were PFS in 2 subgroups of the adenocarcinoma population: patients with eLDH, and patients with mKRAS (a patient may

belong to one or both groups). Key secondary endpoints were to compare the PFS and OS in all adenocarcinoma histology patients, as well as assessment of safety, and comparison of response rate. At the time of randomization, patients were stratified based on PS (ECOG 0 vs. 1), baseline total LDH (normal vs. elevated), smoking status (never-smoker, current, or former smoker), and interval since diagnosis of advanced NSCLC ($\leq$6 vs. >6 months). Time since diagnosis of advanced disease >6 months (determined by date of pathological reports) is indicative of sensitivity to prior chemotherapy and biological behavior of the disease, and this parameter was utilized to balance the treatment arms with respect to patients with more favorable prognosis.

For each of the primary endpoint subgroups, analyses were done at the 1-sided 0.05 level using Bonferroni adjustments for multiplicity (overall Type I Error was set at 0.10). If both analyses were significant, each of the key secondary analyses was to be tested at the 1-sided, 0.05 level. If only one of the primary analyses was significant, each of the two secondary analyses was to be performed at the 1-sided 0.025 level, and if no primary results were significant then secondary analyses would be performed as exploratory. For the eLDH and mKRAS subgroups with an estimated sample size of 120 and 80 patients each, respectively, the study had 90% power to detect a PFS HR of 0.5 favoring the combination arm, using a 1-sided stratified long rank test at the 5% significance level. For the overall adenocarcinoma group with a sample size of 240 patients, there was 88% power to detect PFS HR of 0.67 using a 1-sided stratified log rank test at the 5% significance level. The Cox proportional hazards (PH) model was used to estimate the unadjusted HR using only treatment in the model. To account for factors in the study in addition to treatment, the adjusted HRs were estimated using a stepwise Cox PH regression procedure, where treatment was included in all models. To enter the multivariate model, the prognostic

factor had to be significant in a univariate model ($P \leq 0.10$), and to stay in the multivariate model the factor had to remain significant in the presence of all other factors ($P < 0.20$). Potential prognostic factors included sex, age, total baseline target lesion size, geographic region, and stratification factors, including time since diagnosis of advanced NSCLC (≤6m, >6m). All analyses were conducted by the sponsor using SAS® version 9.3.

Results

Patient Baseline Characteristics

From July 2011 to May 2013, a total of 385 patients were enrolled and 381 received study treatment. Details regarding patient enrollment are provided in the CONSORT diagram (Figure 1). In the adenocarcinoma population (N=253), baseline characteristics were balanced with the exception of a slightly higher representation of women and patients from the US and Western Europe in the combination arm (Table 1). Never-smokers accounted for 25% (63/253) of the patients enrolled. Nearly 95% (241/253) of patients had received a prior platinum-based chemotherapy regimen and the use of prior pemetrexed in combination with platinum therapy was low at 23% (59/253). Seventy percent (177/253) of patients enrolled belonged to the >6 months from advanced NSCLC diagnosis group. Nine percent (11/125) and 14% (18/128) of the patients in the combination and control arms, respectively, had a history of brain metastasis. The median number of metastatic sites was comparable between the study arms (4 vs. 4). The number of patients with tumors harboring EGFR mutations was comparable between study arms (8 vs. 8) as was the number of wt EGFR patients (33/125 vs. 32/128). For the remainder of the patients there was insufficient tumor tissue to determine EGFR status.

Treatment delivery

Out of the 253 adenocarcinoma patients enrolled, 123 in the combination arm and 126 in the control arm received at least one dose of study treatment. Patients in the combination arm received more cycles of treatment (median of 6 cycles) than patients in the control arm (median of 4 cycles): ≥4 cycles (*N*=88, 72% vs. *N*=79, 63%), and ≥8 cycles of treatment (*N*=50, 41% vs. *N*=25, 20%). Forty patients (33%) received ganetespib as monotherapy after the combination regimen was completed.

Safety

The most common Grade ≥3 AEs for treated adenocarcinoma patients (*N*=249) were (combination vs. control): neutropenia 41% (50/123) vs. 42% (53/126), leukopenia 10% (12/123) vs. 6% (7/126), anemia 8% (10/123) vs. 2% (2/126) and neutropenia with fever 9% (11/123) vs. 5% (6/126) (see Table 2 for details). Diarrhea was more common with the use of ganetespib and the majority of episodes were Grade 1 or 2. Diarrhea occurred in the first 24-48 hours after the infusion of ganetespib and was managed with anti-motility agents. Dose reduction due to adverse events occurred in 23/123 (19%) and 13/126 (10%) patients in the combination and control arms, respectively. Discontinuation of study treatments due to serious adverse events (SAEs) was higher with combination therapy (*N*=11, 9% vs. *N*=6, 5%). Serious treatment-related AEs leading to hospitalization occurred in 20 (16%) and 7 (6%) of the patients in the combination and control groups, respectively. The difference in treatment-related SAEs leading to hospitalization is mainly attributed to increased rates of febrile neutropenia (combination vs. control; 10 vs 4 patients), diarrhea-related AEs (4 vs. 0), neutropenia (1 vs. 2), pneumonia (2 vs. 1) and hemoptysis (1 vs. 0). Deaths during study treatment, regardless of attribution, occurred in 21

(17%) and 16 (13%) patients, respectively, for the combination and control arms; such events were assessed as treatment related in 1 patient in the control group.

Efficacy

In the adenocarcinoma population 205 PFS events and 190 OS events had taken place at the time of the final analysis with a median follow up of 22.3 months (m).

None of the endpoints met the prespecified statistical significance, and all secondary analyses were conducted as exploratory in nature. For patients with eLDH (*N*=114), median PFS was similar in both study arms; 2.9 m (90% confidence interval [CI]: 1.7, 3.9) with combination therapy compared to 2.7 m (90% CI: 1.4, 3.7) with control (adjusted PFS HR=0.77, [90% CI: 0.54, 1.10], 1-sided *P*=0.1134) (Figure 2A). The OS analysis showed a trend towards improvement with the combination therapy median at 6.8 m (90% CI: 4.3, 8.1) vs. control at 4.4 m (90% CI: 3.7, 5.8) (adjusted OS HR=0.72, [90% CI: 0.51, 1.01], 1-sided *P*=0.0571) (Table 3).

For patients with mKRAS (*N*=89), the combination treatment did not result in improved PFS (combination median 3.9 m [90% CI: 2.9, 4.2] vs. control 3.0 m [90% CI: 2.7, 4.2], adjusted PFS HR=1.11, [90% CI: 0.74, 1.66], *P*=0.3384) (Figure 2B) or OS (combination median 7.6 m [90% CI: 5.2, 10.7] vs. control 6.4 m [90% CI: 5.2, 11.9], adjusted OS HR=1.23, [90% CI: 0.81, 1.87], *P*=0.2041). Nineteen patients in the combination arm and 16 patients in the control arm were both eLDH and mKRAS positive and were included in both analyses.

For the adenocarcinoma population (*N*=253), the combination arm showed a trend towards improved PFS (median PFS 4.5 m [90% CI: 4.1, 5.5] vs. control median PFS 3.2 m [90% CI: 2.8, 4.1], adjusted PFS HR=0.82, [90% CI: 0.65, 1.03], *P*=0.0784) (Figure 3A). There was also a

favorable OS trend with a median of 10.2 m (90% CI: 8.0, 12.3) for the combination arm compared to 8.4 m (90% CI: 6.3, 10.9) in the control arm (adjusted OS HR=0.84, [90% CI: 0.66, 1.07], *P*=0.1139) (Figure 3B). This analysis did not include the 61 additional patients who were enrolled specifically for the co-primary endpoint analysis.

For the adenocarcinoma population Cox PH models for OS were fit for each of the prespecified stratification factors with only treatment, stratification factor, and the interaction between them in the model. Out of the four models fit, only the parameter estimate for the interaction term of treatment and time since diagnosis of advanced NSCLC was significant (*P*=0.0367) indicating that patients who were diagnosed with advanced NSCLC >6 months prior to study entry received a different benefit from the combination treatment than did those diagnosed ≤6m prior to study entry (Table 3). For the 177 patients in the subset of patients diagnosed >6m prior to study entry, median PFS for the combination and control groups were 5.3 m (90% CI: 4.3, 5.9) and 3.4 m (90% CI: 2.8, 4.2) respectively (adjusted PFS HR=0.74, [90% CI: 0.55, 0.99], *P*=0.0417) (Figure 4A). The median OS was 11.0 m (90% CI: 9.1, 14.5) and 7.4 m (90% CI: 5.8, 10.0) respectively, favoring the combination group (adjusted OS HR=0.69, [90% CI: 0.51, 0.93], *P*=0.0191) (Figure 4B). Baseline characteristics of this subgroup were similar to those of the overall patient population. Conversely, adenocarcinoma patients who were diagnosed with advanced NSCLC ≤6-months prior to study entry (*N*=76) did not receive any treatment benefit from the combination in either PFS (combination median 2.8 m [90% CI: 1.6, 4.2] vs. control median 3.0 m [90% CI: 2.7, 5.4], adjusted PFS HR=0.87, [90% CI: 0.57, 1.39] *P*=0.3280) or OS (combination median 6.2 m [90% CI: 3.7, 11.5] vs. control median 10.2 m [90% CI: 4.9, 13.3], adjusted OS HR=1.01, [90% CI: 0.63, 1.62], *P*=0.4805).

In the adenocarcinoma population, 65/123 (53%) of the patients in the combination group received post study treatment therapy compared to 58/126 (46%) for patients in the control arm. Commonly used agents included erlotinib, etoposide, vinorelbine, cisplatin, gemcitabine, pemetrexed, and a taxane. Patient-reported quality-of-life (QoL) measures, using the EORTC QLQ-30 scale, version 3.0, were not different between groups. The percentages of evaluable questionnaires were 100% at baseline and 75% at end of treatment for the combination arm, 98% at baseline and 72% at end of treatment for the control arm. Baseline Global health status/QoL had a mean of 58.9 (SD 20.85) for the combination group, and a mean of 57.5 (SD 24.51) for the control group. The average change in the QoL from baseline to end of treatment was -5.8 (SD 20.56) for combination patients, and -2.2 (SD 18.65) for docetaxel patients.

Discussion

The goal of this large randomized Phase 2 study was to evaluate efficacy and safety of ganetespib in combination with docetaxel for second-line therapy of advanced NSCLC and to identify patient subgroups that could benefit from this combination therapy. The study did not meet its primary endpoints of improvement in PFS for eLDH or mKRAS patients, however, trends of improvements in ORR, PFS, and OS were observed in adenocarcinoma patients. The strongest signal of efficacy was seen in the exploratory analysis of the large subset of adenocarcinoma patients diagnosed with advanced NSCLC >6 months prior to study entry (~70% of the total adenocarcinoma population).

One possible explanation for the observed lack of efficacy in the mutant KRAS patient population was that the weekly dosing schedule for ganetespib might have been insufficient to durably suppress oncogenic KRAS signaling. To address this potential issue, future trials in this

patient subset should utilize alternate, more frequent ganetespib dosing schedules. In patients with elevated LDH levels, modest improvements in PFS were observed but failed to reach statistical significance. Interestingly, overall survival in these patients was improved following combination therapy and therefore in the ongoing Phase 3 study (GALAXY-2) OS in eLDH patients has been included as a secondary endpoint. Randomized studies conducted in the salvage-treatment setting of advanced NSCLC have utilized different prognostic criteria to stratify patients, such as best response to prior therapy, time since diagnosis of advanced disease, and time since last chemotherapy. The use of >6 months since diagnosis of advanced disease as a stratification factor was pre-specified and allowed differential evaluation of efficacy in patients with better (>6 months) and worse (<6 months) prognosis. Unlike the treatment effect observed in the >6 month population, no efficacy signal was observed in the group diagnosed <6 months prior to study entry. This finding suggests that mechanisms of resistance to chemotherapy, or underlying aggressive disease, might not be sensitive to mitigation by ganetespib. Indeed, preclinical studies show that the functional mitochondrial caspase pathway is critical to ganetespib's anti-cancer effects (D. Fennell, unpublished observations). Archived tumor tissue was collected in nearly all patients enrolled for the purpose of KRAS mutation testing. The next priority was accorded to EGFR mutation testing, which was only possible in a subset of patients (approximately 30%) due to limited tissue availability. Equal numbers of patients were found to have EGFR mutations in each treatment arm; from the available data, EGFR mutation status was not a determinant of sensitivity to ganetespib. We were unable to test for anaplastic lymphoma kinase (ALK) gene rearrangement due to insufficient tissue. Though ALK is a sensitive client protein for Hsp90, given the low prevalence of this gene rearrangement in NSCLC, it is highly

unlikely that activity in ALK-positive patients alone is adequate to drive the overall efficacy of the study.

Given the broad set of putative targets for Hsp90 inhibition, collection of adequate tumor tissue is critical for future studies. A correlation analysis of clinical outcomes in GALAXY-1 with results from tumor tissue profiling using the Oncoscan assay is underway and will be published separately. The findings from the current study prompted the ongoing confirmatory GALAXY-2 Phase 3 trial, with a sample size of 850, in patients with NSCLC of adenocarcinoma histology, diagnosed with advanced disease >6 months prior to study entry.

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Figure Legends

Figure 1. CONSORT diagram.

Figure 2. Kaplan-Meier plots for PFS in the (A) eLDH and (B) mKRAS populations. CI, confidence interval.

Figure 3. Kaplan-Meier plots for (A) PFS and (B) OS in the adenocarcinoma population. CI, confidence interval.

Figure 4. Kaplan-Meier plots for (A) PFS and (B) OS in the adenocarcinoma population diagnosed >6 months before study entry. CI, confidence interval.